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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,575	10/13/2000	Rima Kaddurah-Daouk	AVZ-007CP3	9336

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EXAMINER	
COVINGTON, RAYMOND K	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,575	KADDURAH-DAOUK ET AL.	
	Examiner	Art Unit	
	Raymond Covington	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,10-18,34-39 and 64-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) __ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10-18,34-39 and 64-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-4, 6-8, 34-39, 75 and 84-132 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enabling for a limited set of nervous system diseases such as those having undesired neuronal activity, e.g. multiple sclerosis and Parkinson's disease, does not reasonably provide enablement for claimed conditions such as fungal infection and aging. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not give any guidance as to the full range of nervous system diseases, which could be treated or prevented using the instant claimed process. In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. The nature of the invention,
2. The state of the prior art,
3. The predictability or lack thereof in the art,
4. The amount of direction or guidance present,
5. The presence or absence of working examples,

6. The breadth of the claims,

7. The quantity of experimentation needed, and

8. The level of the skill in the art.

The terms "nervous system disease", "vitamin" claims 6, 57, 85, 97, 107, 119, "prevention" claim 107, "modulating" claim 132, "human" claims 84,106,128,129, "approved drugs" claim 129 are indefinite too the extent they read on inoperative subject matter. No pathways, modes of action or mechanism are recited.

The instant specification does not give any guidance as to the full range of nervous system diseases that could be treated or prevented using the instant claimed process. In order to practice the claimed invention, one skilled in the art would have speculate which nervous system disease could be treated or prevented using the Creatine derivatives found in the instant claims. The number of possible nervous system diseases embraced by the claims would impose undue experimentation on the skilled art worker. Therefore, the broad terminology treating a nervous system disease is not enabled because the metes and bounds of the diseases, which could be treated or prevented, cannot be ascertained. Likewise, the term vitamin reads on inoperative embodiments and would also require undue

experimentation. The same also applies to the other terms mentioned herein above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claims 129, 130 and 132, the terms "modulating" claims 130, 132, "approved drugs" claim 129 renders the claim indefinite. It is not clear how the disease is affected, i.e. does the compound enhance the disease or retard it. As to claim 129, it is not clear what is meant by an approved drug.

The specification does not give any guidance as to the full range of diseases, which could be treated or prevented using the instant claimed process. In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case, Applicants are claiming a method of treating humans. The nature of the pharmaceutical arts is that there is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant specification does not give sufficient support for use in humans. Reference to mammalian use is inadequate in that there is insufficient support that all mammals are subject to all of the diseases falling within the scope of the recited claims, which may be applicable to humans. In order to practice the claimed invention, one skilled in the art would have speculate which diseases could be treated or prevented using the instant claims. The number of possible diseases embraced by the claims would impose undue experimentation on the skilled art worker. Therefore, the broad terminology is not enabled because the metes and bounds cannot be ascertained.

Claims 1-4, 6-8, 34-39, 75 and 84-132 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of specific nervous system disease, (as demonstrated by the Examples 1-3 in the instant specification at pages 50-55 illustrating models for Huntington's disease, Parkinson's disease, ALS disease) comprising the administration of creatine compounds, does not reasonably provide enablement for the administration of the creatine compound, wherein the administration of the creatine compounds results in;

(a) Elimination of all symptoms associated with a preexisting disease of the nervous system; and

(b) Preventing the occurrence of any or all types of nervous system disease within a subject.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not give any guidance as to full range of diseases, which could be treated or prevented using the instant claimed process.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the present case (1) the breadth of the claims encompass methods for treating a subject afflicted with a nervous system disease, wherein the administration of the creatine compound reduces or eliminates symptoms associated with a preexisting disease of the nervous system, or prevents the occurrence of a nervous system disease within a subject. However, the examples In the specification teach the only the administration of creating compounds In model treatments for Huntington's disease, Parkinson's disease, ALS disease In Example 1-3 of the instant specification to yield positive or negative results; (2) the nature

of the claimed invention cannot be determined In light of the foregoing and without knowing how prevention of the many different types of nervous system disease is achieved via the use of creatine compounds and corresponding analogs or derivatives; (3) and (5) the art and the level of predictability in the art is unpredictable as to: [a] the nature of preventing emergence of different nervous system disease as the specification does not teach the outright prevention of the aforementioned disease, including related symptoms, for which there is not known art-recognized therapy. The many different types of nervous system diseases is not regarded as preventable by those skilled in the art, because there simply is no known cure. In light of the aforementioned context, use of the term "preventing" or "eliminating" in the claimed invention equates to the use of the term "cure" but provides no examples of how the prevention or elimination of such diseases are effectuated; (4) and (6) the inventor provides no guidance beyond the model Examples 1-3 taught in the specification and (7) the existence of working example are limited to aforementioned model examples as described In (6) above as taught in the instant specification. Due to insufficient guidance, lack of working examples to support the broad breadth of claims 1-43, one skilled in the art could not predict how the methods of the claimed invention could prevent nervous system diseases. In light of the preceding discussion, one skilled in the art could

not practice invention without undue experimentation, as the claims fail to correlate reasonably with either the enabling disclosure of the specification and the claims.

Claims 1-4, 6-8, 34-39, 75 and 84-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagenfeldt et al. (Muscle and Nerve, October l 7, 1994, Vol. 10 pages 1236-7), Applicants admission in instant specification page 38, lines 1- 18 and Schulthesis et al. (J. of Neurochemistry, June 1990), 54 (6), 1858-63) Hagenfeldt et al. teaches the oral dosage administration of creatine (CAS Reg No.: 57- 00-1) in a therapeutic use for the treatment of a nervous system disease in human patients, i.e., MELAS syndrome (i.e,, as conventionally known in the art as a nervous system disease associated with mitochondrial myopathies and encephalomypathies categories and defined in the art as mitochondrial disorder characterized by focal or generalized seizures, episodes of transient or persistent neurologic dysfunction resembling strokes, and ragged-red fibers In muscle biopsy" as defined by the National Library of Medicine: IGM Metathesaurus information Screen). In view of the above, Hagenfeldt et al. differ from the claimed invention In that it does not teach the use of creatine ln the methods of treatment nervous system disease other than

MELA syndrome. However, it is conventionally known in the art that nervous system disease include: Alzheimer's disease, Parkinson' disease, Huntington's disease, motor neuron disease diabetic and toxic neuropathies, traumatic nerve injuries, multiple sclerosis, acute disseminated encephalomyelitis, amyotrophic lateral sclerosis, acute necrotozong hemorrhagic

leucoencephalitis, diseases of dysmyelination, mitochondrial diseases, fungal and bacterial infections, migrainous disorders stroke, aging, dementia and mental disorders such as depression and schizophrenia as taught by applicants own specification (see instant specification page 9, lines 13-23 to page 16, lines 1-13), Stedman's Medical Dictionary and Medline.

Schulthiess et al. teaches that studies with creatine In complex neuronal systems are of importance, because they show that creatine changes neuronal energy balance and synthesis and release of the neurotransmitter GABA. (Moreover, an admission In applicants instant specification at page 38, lines 1-18, states that the mechanisms by which nerve cell metabolites are normally directed to specifc cell tasks is poorly understood. it is though that nerve cells, like other cells regulate the rate of energy production in response to demand. The creatine kinase system is active in many cells of the nervous system and is thought

to play a role in the allocation of high-energy phosphate to many diverse neurological processes. .")

A person of ordinary skill in the art would have been motivated to develop methods of treating a subject afflicted with a nervous system disease other than MELAS syndrome comprising the administration of creatine, because Schulthiess et al. renders obvious that studies with creatine in complex neuronal systems are of importance, because they show that creatine changes neuronal energy balance and synthesis and release of the neurotransmitter GABA. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Hagenfedt et al. With the teachings of Schulthiess et al. to administer creatine In methods of treating different nervous system diseases that are conventionally known in the art, because creatine would be useful In the treatment of other nervous system disease as al mechanisms of action of the same compound would invariable be inherent.

Claims 1-4, 6-8, 10-18, 34-39 and 64-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jennings WO 94/17794.

Jennings WO $794 teaches Creatme compounds of the type recited in compositions. See, for example, page 1 lines 6+. Patentees do not teach using the

creatine compounds in conjunction with an ATP enhancing agent. However such agents, such as Riluzole, Permax, Sinmet etc., are well-known ATP enhancing agents and are also well-known for use in treating, for example, Alzheimer's disease. It would have been obvious to one of ordinary skill in the art to modify a treatment involving the use of Jennings WO .794 to include other well-known agents for treating the same condition as the results, a cumulative effect, would not have been unexpected. Applicants' comments have been noted and considered, however the rejection is maintained for reasones of record. It is noted that the products per se are known and obvious in the prior artfurther, the cited reference includes within its scope the claimed use. The use of somewhat different but otherwise analogous compositions in an other known method would have been obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond Covington whose telephone number is (703) 308-4704. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. McKane can be reached on (571) 272-0699. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond Covington

Examiner

Art Unit 1625

RKC

RITA DESAI
PRIMARY EXAMINER